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Link to Claims Section

January 5, 1999

Method and apparatus for implementing parallel operations in a database management system

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CORE TERMS: row, slave, processing, scan, message, tree, query, node, scheduler, queue, partitioning, input, ready, parallelism, join, parallelizer's, started, fetch, merge, implemented, rowid, execute, consumer, disk, resume, send, bit, partition, partial, architecture

ENGLISH-ABST:

The present invention implements parallel processing in a Database Management System. The present invention provides the ability to locate transaction and recovery information at one location and eliminates the need for read locks and two-phased commits. The present invention provides the ability to dynamically partition row sources for parallel processing. Parallelism is based on the ability to parallelize a row source, the partitioning requirements of consecutive row sources and the entire row source tree, and any specification in the SQL statement. A Query Coordinator assumes control of the processing of a entire query and can execute serial row sources. Additional threads of control, Query Server, execute a parallel operators. Parallel operators are called data flow operators (DFOs). A DFO is represented as structured query language (SQL) statements and can be executed concurrently by multiple processes, or query slaves. A central scheduling mechanism, a data flow scheduler, controls a parallelized portion of an execution plan, and can become invisible for serial execution. Table queues are used to partition and transport rows between sets of processes. Node linkages provide the ability to divide the plan into independent lists that can each be executed by a set of query slaves. The present invention maintains a bit vector that is used by a subsequent producer to determine whether any rows need to be produced to its consumers. The present uses states and a count of the slaves that have reached these states to perform its scheduling tasks.

PARENT-PAT-INFO:

This is a continuation of application Ser. No. 08/441,527, filed May 15, 1995, now abandoned, which is a

continuation of application Ser. No. 08/127,585, filed Sep. 27, 1993.

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Pharmaceutical Technology

November 2003

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HEADLINE: A review of mouth dissolving tablet technologies

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ABSTRACT

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced-liquid-intake diets have difficulty swallowing these dosage forms. The problem can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration because they dissolve in saliva and do not require water for swallowing. Besides delivering drug to the body, a drug delivery system aims to improve patient compliance and convenience, and mouth dissolving tablets are no exception. Mouth dissolving tablets are mainly designed for pediatric and geriatric patients, which constitute a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of mouth dissolving tablets, which in turn prolongs the patent life of a drug. With continued innovations to pharmaceutical excipients, one can expect the emergence of more novel technologies for mouth dissolving tablets in the days to come.

FULL TEXT

In addition to successfully delivering a drug to the body, the goal of any drug delivery system is to improve patient compliance, and mouth dissolving tablets are no exception. These rapidly disintegrating and dissolving solid dosage forms release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration-an attribute that makes the tablets highly attractive for patient groups such as children and the elderly. In this article, the authors review the various technologies involved in the manufacture of rapidly dissolving tablets.

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative,

nauseated, or on reduced-liquid-intake diets have difficulty swallowing these dosage forms. Elderly patients may find the administration of these dosage forms particularly difficult because many of them are required to consume medicines on a regular basis to maintain their quality of life (1,2). Children also may have difficulty ingesting these dosage forms because of their underdeveloped muscular and nervous systems (3). Swallowing conventional tablets can be further hindered by conditions such as unavailability of water, allergic reactions, and episodes of coughing.

The aforementioned problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration because they dissolve in saliva and do not require water for swallowing. Administration is simple: The tablet is placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed (4).

Innovators and inventor companies have given these tablets various names such as mouth dissolving, fast-melting, fastdissolving, or orodisperse. (The European Pharmacopoeia defines the term orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing [5].) For the purposes of this article, these tablets will be referred to as mouth dissolving. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics, and drugs for erectile dysfunction (6).

Ideal properties of mouth dissolving tablets

The performance of a mouth dissolving tablet depends on the technology used during their manufacture. The necessary property of such tablets is the ability to rapidly disintegrate and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable the mouth dissolving tablet to perform this unique function. An ideal mouth dissolving tablet should meet the following criteria:

* does not require water for oral administration yet disintegrates and dissolves in the mouth within a few seconds

* has sufficient strength to withstand the rigors of the manufacturing process and postmanufacturing handling

* allows high drug loading

* has a pleasant mouthfeel

* is insensitive to environmental conditions such as humidity and temperature

* does not leave any residue in the mouth after disintegration

* is adaptable and amenable to existing processing and packaging machinery

* is cost-effective.

Mouth dissolving tablets offer advantages over other dosage forms such as effervescent tablets, dry syrups, chewing gums, or chewable tablets, which are commonly used to enhance patient compliance. Administering effervescent tablets or granules and dry syrups involve unavoidable preparation that includes the intake of water. Elderly patients cannot chew large pieces of gum or tablets and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste-masking coating ruptures during mastication.

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing mouth dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. As is often the case, a technology that is originally developed to address a particular administration need can quickly become adopted as part of a pharmaceutical company's product life cycle management strategy, which is precisely what has happened with mouth dissolving tablet technologies (see Table I).

Various technologies used in the manufacture of mouth dissolving tablets include

* freeze-drying or lyophilization

* molding

* direct compression

* the cotton-candy process

* spray drying

* sublimation.

Freeze-drying or lyophilization

Freeze-drying is a process in which water is sublimed from the product after it is frozen. This technique forms the basis of Zydis, Quicksolv, and Lyoc technologies, which are used to manufacture rapidly dissolving tablets (7).

Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolved rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin (8). Corveleyn and Remon studied various formulation and process parameters by using hydrochlorthiazide as a model drug (9), on the basis of which US Patent 6,010,719 was granted (10).

R.P. Scherer (Swindon, UK) developed Zydis technology on the basis of a patent granted to Gregory et al. (11,12) and Yarwood et al. (13). Zydis technology is used for drugs such as famotidine, loperamide, piroxicam, oxazepam, lorazepam, domeperidone, brompheniramine, olanzepine, ondenserton, and rizatriptan.

The potential drug should have a particle size 50 [mu]m (14,15). For a water-soluble drug, the dose should not exceed 60 mg, and for a water-insoluble drug, the maximum drug limit is 400 mg.

Mouth dissolving tablets that are manufactured using lyophilization usually contain the following excipients:

* polymers (e.g., gelatin, alginates, and dextrin), which provide strength and rigidity to a tablet

* polysaccharides (e.g., mannitol and sorbitol), which impart crystallinity and hardness to the matrix and improve palatability

* collapse protectants (e.g., glycine), which prevent a product from shrinking in its packaging during manufacture and storage

* flocculating agents (e.g., xanthan gum and acacia), which provide uniform dispersion of drug particles

* preservatives (e.g., parabens), which prevent microbial and fungal growth

* permeation enhancers (e.g., sodium lauryl sulfate), which help improve transmucosal permeability

* pH adjusters (e.g., citric acid or sodium hydroxide), which optimize chemical stability

* flavors and sweeteners, which improve patient compliance

* water that ensures formation of porous units.

The manufacture of mouth dissolving tablets using lyophilization involves a series of procedures. First, the active drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through a liquid-nitrogen freezing

tunnel to freeze the drug solution or dispersion. Then, the frozen blister packs are placed in refrigerated cabinets to continue the freezing process, and afterward they are subjected to freeze-drying. After freeze-drying, the aluminum foil backing is applied on a blister-sealing machine. Finally, the blisters are packaged and shipped.

Although this process may seem fairly routine, lyophilization is relatively expensive and time-consuming. Other disadvantages of lyophilized products include fragility, which makes conventional packaging unsuitable for these products, and poor stability of the product under stressed conditions.

Tablet molding

Molded tablets invariably contain water-soluble ingredients so the tablets dissolve completely and rapidly. The active ingredient in most cases is absorbed through the mucosal lining of the mouth.

The manufacturing process of molding tablets involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mold plates to form a wetted mass (compression molding). The solvent is then removed by air drying. Thus the process is similar to what is used in the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug (16). The heat-molding process uses an agar solution as a binder and a blister-packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister-packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at ~30 [degrees]C under vacuum.

Another process used is called no-vacuum lyophilization, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure. Pebley et al. evaporated a frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth, or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin), and a solvent in a tablet-shaped mold (17).

Tablets produced by molding are solid dispersions. The drug, depending on its solubility in the carrier, exists as discrete particles or microparticles dispersed in the matrix, is dissolved totally to form a solid solution, or is dissolved partially in the carrier. Compared with lyophilization, tablets produced by the molding technique are easier to scale up to industrial manufacture.

Takeda Chemical Industries (Osaka, Japan) developed a compression-molded combination of drug and starch or sugar, with water as a wetting agent. The wet mass is compression molded then dried and yields porous tablets with sufficient mechanical strength (18).

Direct compression

Direct compression represents the simplest and most cost-effective tablet manufacturing technique. This technique can now be applied to mouth dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.

Disintegrates. In many mouth dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hasten the process.

The introduction of so-called superdisintegrants and a better understanding of their properties have increased the popularity of this technology (19). Tablet disintegration time can be optimized by concentrating the disintegrant. Below critical concentration, tablet disintegration time is inversely proportional to disintegrant concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases (20).

Ethypharm (Saint-Cloud, France) has introduced a Flash dose technology, which contains coated crystals and microgranules along with disintegrants (21). In this technology, two types of disintegrants are used: a disintegrating agent (e.g., modified cellulose), which has a high swelling force, and a swelling agent (e.g., starch), which has a low swelling force (22).

Bi et al. (23) and Watanbe et al. (24) used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture rapidly disintegrating tablets. The ratios of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihara investigated applying agar powder as a disintegrant because the powder absorbs water and swells considerably without forming a gel at physiological temperatures (25).

The evolution of carbon dioxide as a disintegrating mechanism, which forms the basis of OraSolv technology, is described in a US patent assigned to Cima Labs (Eden Prairie, MN) (26,27). The product is slightly effervescent and contains multi-particulates. Saliva activates the effervescent agent, causing the tablet to disintegrate. DuraSolv, a second-generation technology developed by Cima Labs, also has been used in the production of robust, mouth dissolving tablets.

The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected in the overall cost of the product. Tempra Quicklets (Bristol-Myers Squibb, New York, NY), which contain 80 mg of paracetamol in each tablet, and Zomig Rapimelt (Astra Zeneca International, Wayne, PA), which contain zolmitriptan, are mouth dissolving tablets that contain effervescent agents.

A combination of alginic acid and water-soluble metal carbonic acid has been suggested by Michaelson (28). An acid-base reaction takes place when the tablet is placed in the aqueous medium, forming metal alginate and carbonic acid. The salt causes swelling of the tablet, and the carbon dioxide generated leads to disintegration of the tablet.

Sugar-based excipients. Another approach to manufacturing mouth dissolving tablets by direct compression is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose, and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and a pleasing mouthfeel. Mizumoto et al. have classified sugar-based excipients into two types on the basis of their moldability and dissolution rate (29). Type I saccharides (e.g., lactose and mannitol) exhibit low moldability but a high dissolution rate. Type II saccharides (e.g., maltose and maltitol) exhibit high moldability but a low dissolution rate. Moldability in this respect is defined as the capacity of the compound to be compressed (molded) and to dissolve and does not refer to the formation of a true molding by melting or solvent wetting.

The moldability of a Type I saccharide can be improved by granulating it with a Type II saccharide solution. Yamanouchi Pharma Technologies (Palo Alto, CA) developed WOWTAB on the basis of this technology (30), which involves using fluidized-bed granulation for the surface treatment of a Type I saccharide with a Type II saccharide. WOWTAB technology is the basis for Benadryl Fastmelt tablets.

Daiichi Pharmaceutical Co. (Tokyo, Japan) conducted a series of experiments to develop a mouth dissolving tablet using a combination of starch or cellulose and one or more water-soluble saccharides (31). Erythritol was found to be the best saccharide because it displayed rapid disintegration, good tolerability and sweetening, and a refreshing mouthfeel as a result of its negative heat of solution.

Cotton-candy process

The cotton-candy process is also known as the candy floss process and forms the basis of technologies such as FlashDose (Fuisz Technologies, Chantilly, VA). A mouth dissolving tablet is formed using a candy floss or shearform matrix (32,33). The matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force (34-38). The matrix is then cured or partially recrystallized to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended

with active ingredients and other excipients and subsequently compressed into mouth dissolving tablets. The technology also can be used to form microspheres instead of floss by modifying the design of the spinning heads.

A tablet made with FlashDose technology can accommodate high doses of drug and possesses satisfactory mechanical strength. However, the high processing temperature limits the use of this technology to thermostable compounds only.

Spray-drying

Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen et al. have reported applying this process to the production of mouth dissolving tablets (39-42). The formulations that were produced contained hydrolyzed and unhydrolyzed gelatin as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray-dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 s in an aqueous medium.

Sublimation

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate a porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea, and urethene) were compressed along with other excipients into a tablet (43-45). The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generating porosity in the matrix.

Koizumi et al. applied sublimation technology to manufacture tablets that rapidly dissolve in saliva (46). Mannitol was used as a matrix former, and camphor was used as a subliming agent. The tablets dissolved in 10-20 s and displayed satisfactory handling properties. Makino et al. reported a method using water as a pore-forming material (47). A mixture of drug and a carbohydrate (e.g., erythritol, glucose, maltitol, sucrose, or xylitol) was wetted using 1-3% water and compressed into tablets. The water was then removed, yielding highly porous tablets with satisfactory mechanical strength and a high dissolution rate.

Conclusion

Besides delivering drug to the body, a drug delivery system aims to improve patient compliance and convenience, and mouth dissolving tablets are no exception. Mouth dissolving tablets are mainly designed for pediatric and geriatric patients, which constitute a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of mouth dissolving tablets, which in turn prolongs the patent life of a drug. With continued innovations to pharmaceutical excipients, one can expect the emergence of more novel technologies for mouth dissolving tablets in the days to come.

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GRAPHIC: Tables
IMAGE TABLE, Table I: Various technologies used in the manufacture of mouth dissolving tablets and the companies that invented them.

LOAD-DATE: August 15, 2007

Patent Search 5857180 6/22/2010

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Search: (US5857180)/PN/XPN

1 / 1 **Patent Number:** US5857180 A 19990105

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20030909	US/RF-A [OPP]	REISSUE APPLICATION FILED EFFECTIVE DATE: 20020522
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E8	1	PN=US 5857351
E9	1	PN=US 5857441
E10	1	PN=US 5857509